REMARKS

The remainder of this Reply appears appropriate subheadings for the convenience of the Examiner.

Claim Amendments

Claim 5 was amended to more clearly define Applicants' claimed invention. Support for amendments to the claims can be found throughout the specification and previously amended Claim 5. No new matter has been added. Entry is requested.

Rejection of Claim 5-7 and 12-14 For New Matter

The Examiner stated that the specification lacked support for the phrases "spondyloepiphyseal dysplasia," "congenita skeletal dysplasis" and "multiple epiphyseal dysplasia" and that such phrases were considered new matter.

As a preliminary matter, Applicants' claimed invention, as set forth in independent Claim 5 is directed to a method of treating a patient having at least one pathology selected from the group consisting of a bone fracture, a congenital condition due to poor or retarded growth or ossification, spondyloepiphyseal dysplasia congenita, skeletal dysplasia, and multiple epiphyseal dysplasia. (Emphasis added). Applicants' claimed invention is not directed to a method of treating "spondyloepiphyseal dysplasia" or "congenita skeletal dysplasia." Further, support for the phrases "spondyloepiphyseal dysplasia," "congenita skeletal dysplasia" and "multiple epiphyseal dysplasia" can be found in the specification at, for example, page 21, lines 23-25, which states:

> Congenital conditions of poor and retarded ossification may included [sic], by way of example only and not of limitation, spondyloepiphyseal dysplasia congenita, skeletal dysplasias, hip dysplasia, and multiple epiphyseal dysplasia.

Thus, the phrases "spondyloepiphyseal dysplasia," "congenita skeletal dysplasia" and "multiple epiphyseal dysplasia" are not new matter. Entry of the claims amendments is requested.

Rejection of Claims 5-7 and 12-14 Under 35 U.S.C. § 112, First Paragraph

Claims 5-7 and 12-14 were rejected under 35 U.S.C. § 112, first paragraph. The Examiner stated that the reasons for the rejection were as set forth on page 2 of the Office Action dated October 7, 2003. On page 2 of the Office Action dated October 7, 2003, the Examiner stated that Claims 5-7 and 12-14 failed to comply with the written description requirement because the claims contained subject matter which was not disclosed in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner further stated that The Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997), was relevant and held that an adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, "not a mere wish or plan for obtaining the claimed invention."

In addition, the Examiner stated that the Federal Circuit has adopted the standard set forth in the Patent and Trademark Office guidelines for examination under the written description requirement published in the Federal Register (66 Fed Reg 1099 (Jan 5, 2001)). In support of this statement, the Examiner cited Enzo Biochem, Inc. v. Gen-Probe, Inc., 296 F.3d 1316 (Fed. Cir. 2002) and stated that a written description can be met by "showing that an invention is complete by disclosure of sufficient detailed, relevant identifying characteristics, including, inter alia, functional characteristics when coupled with a known or disclosed correlation between function and structure." The Examiner further stated that Lilly and Enzo were decided based on DNA sequences, but did not preclude application of the reasoning to cases of chemical structure in general. The Examiner then stated that Applicants' specification failed to provide an adequate written description of a suitable retinoid receptor agonist or the pharmaceutically acceptable salt or ester thereof because Applicants' specification described only a number of retinoic acid antagonists and the specification "quite simply, does not [describe] any agonists."

The Federal Circuit in Lilly, cited by the Examiner, makes clear that mention of a representative number of species encompassed by a generic claim is not required by any statute, including 35 U.S.C. § 112. Lilly at 1569. In particular, in quoting In re Robins, 57 C.C.P.A. 13212, 429 F.2d 452, 456-457, 166 U.S.P.Q. (BNA) 552, 555 (CCPA 1970), the Federal Circuit in Lilly stated:

> Mention of representative compounds encompassed by generic claim language clearly is not required by § 112 or any other provision of the statute. But, where no explicit description of a generic invention is to be found in the specification ... mention of a representative compounds may provide an implicit description upon which to base generic claim language.

Id.

As Applicants discussed in the Reply filed July 20, 2005, Section 2163, page 2100-181 of the August 2005 revised edition of the Manual of Patent Examining Procedure ("MPEP") states that there are several factors to consider when determining the adequacy of the written description of a specification to support claimed subject matter:

> Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

(Emphasis added).

Applicants have adequately described retinoid receptor agonists by, for example, functional characteristics, which alone can be sufficient in order to show that Applicants had possession of the claimed invention, as noted in Section 2163 of the MPEP (*supra*). For example, as discussed in the Reply filed July 20, 2005, retinoid receptor agonists are described in the Applicants' specification. In particular, page 4, lines 25-28, describe retinoid receptors as follows:

> At the molecular level retinoids exert their biological effects through two families of nuclear receptors, retinoic acid receptors (RARs) and retinoid X receptors (RXRs), which belong to the superfamily of steroid/thyroid/vitamin D3 nuclear receptors.

Further, an agonist is defined on page 6, lines 24-25 of Applicants' specification:

> As used herein, "agonist" means a compound that will stimulate the ligand-mediated transactivational activity of the specified retinoid receptor.

In addition, on page 21, lines 17-25 of Applicants' specification, the use of retinoid receptor agonists are explicitly described:

> In another embodiment the instant invention is drawn to the use of retinoid receptor agonists as positive regulators of endochondral ossification. In this embodiment are provided methods for (a) enhancing the reparative process during fracture repair, (b) treating congenital conditions in individuals who may exhibit poor or retarded growth and ossification, (c) ameliorating osteoporosis, and (d) stimulating and modulating intramembrane ossification through treatment with retinoid receptor agonists. Congenital conditions of poor and retarded ossification may included [sic], by way of example only and not of limitation, spondyloepiphyseal dysplasia congenita, skeletal dysplasias, hip dysplasia, and multiple epiphyseal dysplasias.

As discussed above, Applicants' specification defines retinoid receptors, defines agonists and explicitly describes a generic invention in the specification, as set forth in Claims 5-7 and 12-14. The Examiner is correct in stating that "When functional claims are drawn this broadly, they are inclusive of any retinoic acid agonist or pharmaceutically acceptable salt or ester therof." Applicants are not precluded from describing the invention by functional characteristics alone (See, *supra*, quoting the MPEP, section 2163, pages 2100-181) and are entitled to the use of any retinoid receptor agonist in the claimed methods. Applicants are not required to list or describe species of retinoid receptor agonists because of the explicit description of the generic invention in Applicants' specification is sufficient to demonstrate Applicants' possession of the invention as claimed.

Therefore, contrary to the Examiner's statement that the specification does not describe in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention, Applicants' specification provides a written description that conveys with reasonable clarity to those skilled in the art that Applicants were in possession of the claimed invention. Thus, the specification meets the written description requirements of 35 U.S.C. § 112,

first paragraph as applied to Applicants' claimed invention as set forth in Claims 5-7 and 12-14, as amended.

Rejection of Claims 5-7 and 12-14 Under 35 U.S.C. § 102(b)

The Examiner stated that Claims 5-7 and 12-14 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No: 5,070,108, issued to Margolis (hereinafter "Margolis"). The Examiner cited Margolis at column 2, lines 35-42 and 64-68 and stated that Margolis taught the use of retinoids for the gain in mineral loss and to decrease bone fractures. Column 2, lines 35-42 of Margolis states:

> Surprisingly in view of the literature on retinoids described herein, it has been demonstrated by the Applicant that retinoids can reverse the bone mineral loss that occurs in mammals with osteoporosis. It has also been observed that the gain in bone mineral loss appears to be functionally sound and prevents the occurrence of pathologic fractures.

Column 2, lines 64-68 of Margolis states:

> The Applicant has recognized that the use of retinoids in the treatment of osteoporosis would not only reduce the incidence of osteoporosis and increase the mineral content in bone, but as a result would decrease the number of bone fractures due to osteoporosis.

Applicants' claimed invention, as set forth in independent Claim 5, as amended, is directed to a method for treating a patient, comprising the step of administering a therapeutically effective amount of at least one member selected from the group consisting of a retinoid receptor agonist or a pharmaceutically acceptable salt or ester thereof to a patient having at least one pathology selected from the group consisting of a bone fracture, a congenital condition due to poor or retarded growth or ossification, spondyloepiphyseal dysplasia congenita, skeletal dysplasis, and multiple epiphyseal dysplasia. Dependent Claims 6 and 7 further limit the retinoid receptor agonist employed in the method to an RAR receptor agonist and the RAR receptor agonist is an RAR$\alpha\beta\gamma$ receptor agonist, respectively.

Applicants' claimed invention, as set forth in independent Claim 12 is directed to a method for stimulating the healing of a bone fracture in a patient that is in need thereof,

comprising the step of administering to said patient an effective amount of a retinoid receptor agonist or a pharmaceutically acceptable salt or ester thereof. Dependent Claims 13 and 14 further limit the retinoid receptor agonist to an RAR receptor agonist and an RAR$\alpha\beta\gamma$ receptor agonist, respectively.

Margolis describes methods of treating osteoporesis, increasing bone mineral content and preventing the occurrence of compression fractures with retinoids, such as vitamin A in its naturally occurring forms such as retinol, retinal, retinyl esters, retinoic acid as well as synthetic analogs of vitamin A. For example, column 1, lines 8-12 of Margolis states:

> This invention relates to a method of treating osteoporosis. More particularly, methods of treating osteoporosis, increasing bone mineral content and preventing the occurrence of compression fractures with retinoids are provided.

Column 3, lines 4-7 of Margolis states:

> As used herein, the term "retinoids" denotes vitamin A in its naturally occurring forms such as retinol, retinal, retinyl esters, retinoic acid as well as synthetic analogs of vitamin A.

Margolis does not teach or suggest a method for treating a patient, comprising the step of administering a therapeutically effective amount of at least one member selected from the group consisting of a retinoid receptor agonist or a pharmaceutically acceptable salt or ester thereof to a patient having at least one pathology selected from the group consisting of a bone fracture, a congenital condition due to poor or retarded growth or ossification, spondyloepiphyseal dysplasia congenita, skeletal dysplasis, and multiple epiphyseal dysplasia, as set forth in Applicants' Claim 5. Margolis does not teach or suggest the use of an RAR receptor agonist or an RAR$\alpha\beta\gamma$ receptor agonist in the method of claims, as set forth in Claims 6 and 7 of Applicants' invention. In addition, Margolis does not teach or suggest a method for stimulating the healing of a bone fracture in a patient that is in need thereof, comprising the step of administering to said patient an effective amount of a retinoid receptor agonist or a pharmaceutically acceptable salt or ester thereof, as set forth in Applicants' Claim 12 or the use of an RAR receptor agonist and an RAR$\alpha\beta\gamma$ receptor agonist in a method of healing a bone fracture, as set forth in Claims 13 and 14 of Applicants' invention. Therefore, Margolis does not anticipate Applicants' claimed invention, and Claims 5-7 and 12-14 meet the requirements of 35 U.S.C. § 102(b).

Further, Margolis was cited by the Examiner in a rejection of, in part, Claims 5-7 and 12-14 under 35 U.S.C. § 103 in an Office Action mailed on February 14, 2001. Applicants filed a reply to the February 14, 2001, Office Action on May 14, 2001. In an Office Action Made Final, mailed July 23, 2001, the Examiner maintained the rejection under 35 U.S.C. § 103 in view of Margolis. Applicants filed a Reply to the Office Action Made Final on October 23, 2001. The Examiner mailed an Advisory Action on January 31, 2002, maintaining the rejection for "reasons of record." Applicants subsequently filed a Continued Prosecution Application on April 24, 2002. In an Office Action mailed March 10, 2003, the Examiner made no mention of Margolis. Applicants filed a Reply to the March 10, 2003, Office Action on July 10, 2003, and the Examiner mailed an Office Action on October 7, 2003, rejecting Claims 5-7 and 12-14 based only on 35 U.S.C. § 112, first paragraph as lacking an adequate written description. Applicants filed a Reply to the October 7, 2003, Office Action on February 5, 2004. In a subsequent Office Action mailed August 5, 2004, the Examiner maintained the written description rejections "for the reasons set forth on page 2 of the office action of October 7, 2003." Applicants filed a reply to the August 5, 2004, Office Action on July 20, 2005. In an Office Action mailed September 8, 2005, to which this Reply in being filed in response to, now rejects Claims 5-7 and 12-14 under 35 U.S.C. § 102(b) as being anticipated by Margolis.

In view of the Examiner's rejection over five (5) years ago of Claims 5-7 and 12-14 as obvious in light of Margolis, the apparent withdrawal of the obviousness rejection and the lack of any rejection of Claims 5-7 and 12-14 under 35 U.S.C. § 102 in view of Margolis in three (3) Office Actions over a period of three (3) years, the recent mailing of an Office Action that now rejects Claims 5-7 and 12-14 under 35 U.S.C. § 102(b) in view of Margolis, which was not prompted by any amendment of Applicants over a five (5) year period, is a cause of concern to Applicants regarding the pace of prosecution. Section 707.07(g) of the Manual of Patent Examining Procedure (8th edition, August 2001, Revised August 2005) (hereinafter "MPEP") states:

> Piecemeal examination should be avoided as much as possible. The examiner ordinarily should reject each claim on all valid grounds available, avoiding, however, undue multiplication of references.

Applicants respectfully request withdrawal of this rejection for this reason and, moreover, because Applicants' claimed invention, as set forth in Claims 5-7 and 12-14, is not anticipated by Margolis and meets the requirements of 35 U.S.C. § 102(b).

SUMMARY AND CONCLUSION

Claims 5-7 and 12-14 do not contain new matter. The specification provides an adequate written description to support Claims 5-7 and 12-14, as amended, by meeting the requirements of 35 U.S.C. § 112, first paragraph. Claims 5-7 and 12-14 meet the requirements of 35 U.S.C. § 102(b). If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the Applicants' undersigned attorney.

Respectfully submitted,

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